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(71) Applicant (for AE, AG, AU, BB, BZ, CA, CY, GB, GD, GH, GM, IE, IL, KE, LC, LK, LS, MN, MW, NZ, OM, SD, SG, SI, SZ, TT, TZ, UG, ZA, ZM, ZW only): **UNILEVER PLC** [GB/GB]; Unilever House, Blackfriars, London EC4P 4BQ (GB).

(71) Applicant (for all designated States except AE, AG, AU, BB, BZ, CA, CY, GB, GD, GH, GM, IE, IL, IN, KE, LC, LK, LS, MN, MW, NZ, OM, SD, SG, SI, SZ, TT, TZ, UG, ZA, ZM, ZW): **UNILEVER NV** [NL/NL]; Wcena 455, NL-3013 AL Rotterdam (NL).

(71) Applicant (for IN only): **HINDUSTAN LEVER LIMITED** [IN/IN]; Hindustan Lever House, 165/166 Backbay Reclamation, Maharashtra, 400 020 Mumbai (IN).

(72) Inventors: **McGLONE, Francis**; Unilever Research Port Sunlight, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **PATERSON, Sarah**; Unilever Research Port Sunlight, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **RWLINGS, Anthony, Vincent**; Unilever Research Port Sunlight, Quarry

Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **RUKWIED, Roman**; Unilever Research Port Sunlight, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **WATKINSON, Allan**; Unilever R & D Colworth, Colworth House, Sharnbrook, Bedford, Bedfordshire MK44 1LQ (GB).

(74) Agents: **PEARCE, Timothy et al.**; Unilever Plc, Patent Department, Colworth House, Sharnbrook, Bedford, Bedfordshire MK44 1LQ (GB).

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(54) Title: **ANTIPERSPIRANT OR DEODORANT COMPOSITIONS**

(57) Abstract: Deodorant and antiperspirant compositions comprising an aluminium or aluminium-zirconium active can suffer from perceived irritancy when applied topically, which is generally manifested as an itch sensation. This irritancy can be ameliorated or overcome by incorporating within the composition a cannabinoid receptor (CBR) activating agent, and especially an amount selected in the range of from 0.25 to 10 wt. %.

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ANTIPERSPIRANT OR DEODORANT COMPOSITIONS

The invention relates to antiperspirant or deodorant
5 compositions intended for topical application to human skin.
In particular, it relates to antiperspirant or deodorant
compositions comprising an agent that is capable of
ameliorating or controlling skin irritancy

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Background

In many countries, civilised behaviour encourages people to
take steps to prevent or control body odours or visible wet
15 patches caused by sweating, particularly in the underarm or
on clothing in the vicinity of the underarm. People in some
countries prefer to control both sweat and odour, whereas in
other countries control of odour alone is favoured.

20 The antiperspirant market is currently dominated by
topically applied products based on aluminium or zirconium
salts which are intended to prevent, or at least control,
localised perspiration at the skin surface, particularly on
the underarm. Such formulations can often simultaneously
25 provide a perceived degree of deodorancy.

In contrast, deodorants are formulations that are designed
either to mask malodour or to prevent or hinder its
formation. The latter method usually comprises reducing
30 and/or controlling the re-growth of the local micro-organism
populations, or targeting preferentially those bacteria such

as a sub-class of Coryne bacteria which contribute disproportionately to axillary odour generation, or interrupting the pathways by which malodours are formed from secretions.

5

Antiperspirant and deodorant formulations are utilised in many applicator forms e.g. roll-ons, creams or soft solids, gels, firm sticks, aerosols and pump sprays. However all forms can suffer from a number of common disadvantages.

10

A principal disadvantage of many deodorants and antiperspirants is that they contain one or more commonly employed ingredients which are perceptibly unfriendly to human skin in those areas of the body to which the formulations are normally applied. Such ingredients are usually employed because they demonstrate other attributes which are advantageous or otherwise render the formulation particularly effective. Such essential or otherwise highly desirable ingredients include liquid carriers such as volatile silicones and ethanol, and indeed many deodorant or antiperspirant actives as well as a host of other ingredients commonly employed in deodorant and antiperspirant formulations. Such ingredients are perceived to exhibit an adverse effect, in particular an irritant effect, on a user's skin following application. Of those ingredients, particular attention may be accorded to aluminium and zirconium salts and complexes that act as antiperspirants.

30

Physiologically, irritation in the underarm usually adopts either or both of two forms, which are not mutually

exclusive. It can manifest itself as redness due to inflammation or as noxious somatosensory responses such as pruritus (itch), sting and/or burn.

- 5 Skin unfriendliness can be tolerated, at least to some extent, which will vary from user to user, but it would be advantageous to identify means of reducing or eliminating the effect. Manifestly, irritation can be ameliorated by lowering the amount of any offending active ingredient in the
10 formulation, but a serious drawback of such an approach is that the efficacy of the ingredient would be impaired.

Rather than look only empirically for materials which can demonstrate skin benefits in an antiperspirant or deodorant
15 formulation, the inventors of the present invention have investigated mechanisms within skin cells which generate irritancy and related adverse skin conditions in humans and have sought means to alleviate or control those mechanisms.

- 20 Mankind has sought therapeutic means to relieve pain and suffering ever since records have been kept. Early remedies involved the administration of natural products, commonly by ingestion, topical application or inhalation, presumably as a result of empirical observations. For example, *Cannabis*
25 *sativa*, colloquially called cannabis, or extracts therefrom, has been employed therapeutically for approximately 3000 years, being first mentioned in the time of Emperor Shen Nung in the *Chinese Compendium of Medicine*. It has subsequently been suggested that its perceived efficacy can
30 be due to the action of Δ^9 -tetrahydrocannabinol. Cannabinoid agents have been asserted to have anti-inflammatory actions

(A.W. Wirth et al., Life Sci. 26, 1991-1995 (1980)). More recent research has shown that the biological actions of cannabis are mediated by two similar, but distinct, types of membrane receptor which have been termed Cannabinoid

5 Receptor 1 (CB1R) and Cannabinoid Receptor 2 (CB2R) (Matsuda et al, Nature 346, 561-564 (1990), Munro et al, Nature, 365, 61-65 (1993)).

CB1R is by far the predominant form in the central nervous
10 system, whereas both CB1R and CB2R are located in the peripheral tissues, including the skin. Some investigations have been made to locate natural endogenous ligands that can activate one or other of these receptors. Herein a reference to a CBR activator includes either or both CB1R and CB2R
15 activators.

Arachidonylethanolamide (anandamide) has been stated to exhibit a greater affinity for the CB1R compared with CB2R and is believed to be the endogenous CB1R agonist (Pertwee et
20 al, Br. J. Pharmacol. 105, 980-984 (1992)). It has been suggested that palmitoylethanolamide and 2-arachidonyl-glycerol are putative CB2R agonists (Facci et al, Proc. Natl. Acad. Sci. 92, 3376-3380 (1995), Sugiura et al., J. Biol. Chem. 275, 605-612 (2000)). Ligands that activate both CB1R
25 and CB2R have been shown to be analgesic, whether applied systemically or cutaneously (Calignano et al, Nature, 394, 277-280 (1998)).

Therapeutic uses have already been contemplated involving
30 CBRs. For example, US-A-5990170 (Della Valle et al) teaches the therapeutic use of a range of selected mono and

dicarboxylic acid amides which bind the CB2R in order to treat diseases connected with this receptor. EP-A-550006 (Della Valle et al) teaches that a range of N-acyl derivatives of amino alcohols to be used for the treatment of pathologies characterised by the degranulation of mast cells. 5 US-A-5679667 describes the use of amino alcohols-N-acyl derivatives as therapeutic agents against neurogenic endoneural edema of the peripheral nerve. However, none of these references disclose or contemplate in any way 10 antiperspirant or deodorant formulations or the use of any of the actives disclosed therein in such formulations.

During the last century, many different classes of compounds have been proposed in patent or other publications for 15 incorporation in antiperspirant or deodorant formulations. However, none of such antiperspirant or deodorant publications have disclosed the subject of the present invention, either knowingly or unwittingly, for example because the compounds that are disclosed in them for other 20 purposes are inactive for the present purpose, even though some of them may be chemically related to an active compound. Alternatively, the selection of ingredients of the instant invention has not been disclosed.

25 Thus, for example, US-A-4781917 (Luebbe et al) describes the use of different monoethanolamides such as coconut mono- or stearamide monoethanolamide in antiperspirant gel sticks that do not exhibit the advantageous properties required for the instant invention. In addition, US-A-5407668 (Kellner) 30 teaches of the use of a class of alkanolamides in clear deodorant stick compositions as a component of a clarity

enhancing solubilizer system, but does not contemplate expressly the presence of aluminium or zirconium antiperspirant salts or complexes. Accordingly, '668 does not teach how to select materials to satisfy the instant invention.

Summary of the Invention

- 10 According to the invention there is provided an antiperspirant or deodorant cosmetic composition suitable for topical application to the human skin, characterised by comprising:
- 15 i. an antiperspirant or deodorant active comprising an aluminium and/or zirconium salt or complex;
 - ii. a carrier for the antiperspirant or deodorant active; and
 - iii. an effective amount of a CBR activating agent.
- 20 By the employment of a CBR activating agent in an effective amount in an antiperspirant or deodorant formulation containing an aluminium and/or zirconium salt or complex, it is possible for users of such formulations to experience reduced or no irritancy such as itch or like skin complaints
- 25 on areas of the skin to which formulation has been applied.

The capability of a compound to act as a CBR activating agent can be determined using a topical application test on human skin in which the irritant effect of a predetermined

30 concentration of a known irritant, for example a known

pruritic agent, such as histamine, is counteracted by chosen amounts of the target compound.

Detailed Description of the Invention and Preferred

5 Embodiments

The present invention relates to the incorporation of a CBR activating agent in antiperspirant or deodorant compositions. The effectiveness of a material to act as a CBR activating agent can be determined by incorporating it in an antiperspirant or deodorant composition and observing the extent to which redness, itch, sting or burn is diminished.

15 It can be convenient to employ a topical application test as a way of demonstrating whether the test material would be effective as a CBR activating agent. In one such test employing the control conditions described subsequently herein, human skin is contacted with a control or test material under a water-impermeable patch for a specified length of time, such as 24 hours and then challenged with a predetermined dose of a known irritant such as histamine applied by iontophoresis at a specified current for a specified period, e.g. 10 seconds at 50 μ A, which is

25 counteracted by application of a test material within a range of concentrations so as to be able to identify that at which the material becomes effective. By plotting the perceived strength of the response against time, a test value can be obtained which comprises the area under the curve. This area is normally that from time 0 to 5 minutes and the base line at 0 to the response curve. In an

30

alternative, but related, test procedure, a cream formulation is applied topically to the skin, for example for a period of 4 hours rather than being covered by a patch, and is then challenged in the same way.

5

The measured activity of test material can vary between subjects. Accordingly, an averaged result should be employed. The test material can be considered to pass the histamine test at its chosen concentration when the averaged
10 test value from histamine plus the test material is less than 80% of the control test value, i.e. that obtained from histamine without the test material under the same test conditions. Preferably, the material and its amount are chosen in combination such that the resultant averaged test
15 value is not higher than 50% of the control test value.

In such a test, the difference necessary for it to be statistically significant decreases as the number of subjects in the test increases. For the most effective CBR
20 activating agents, a small number of subjects can demonstrate a positive result, whereas for less active agents, it is desirable to employ a larger number such as at least 20 subjects and preferably about 50.

25 Herein a material is considered to be a CBR activating agent, if it passes the foregoing test or any other test method for CBRs described herein.

It is particularly desirable to identify and employ a
30 compound that can act as an activating agent for a CBR ie

for either or both CB2R and CB1R, on account of the presence of both CB1R and CB2R sites in skin.

Examples of CBR activating agents (iii) include:-

- 5 2-arachidonyl-glycerol
- 1-arachidonyl-glycerol
- 3-arachidonyl-glycerol
- 2-linoleoyl-glycerol
- 2-linolenoyl-glycerol
- 10 2-eicosatrienoyl-glycerol
- 2-eicosatetraenoyl-glycerol
- 2-eicosapentenoyl-glycerol
- 2-eicosaheptaenoyl-glycerol
- Palmitoylethanolamide
- 15 (6aR)-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol, sometimes called HU-210 herein;
- Indomethacin morpholinylamide sometimes abbreviated to IMMA herein;
- 20 mesylate: (R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone, sometimes called WIN55212-2 herein;
- (-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol, sometimes called CP55940
- 25 herein;
- R-(+)-Methanandamide: [R-(all-Z)]-N-(2-Hydroxy-1-methylethyl)-5,8,11,14-eicosatetraenamide;
- Arachidonyl-2'-chloroethylamide: (all Z)-N-(2-cycloethyl)-5,8,11,14-eicosatetraenamide);
- 30 Arachidonylcyclopropylamide: (all Z)-N-(cyclopropyl)-5,8,11,14-eicosatetraenamide;

It will be understood that, for example, although palmitoyl ethanolamide acts as a CBR activating agent, ethanolamides which are structurally similar, but derived from related aliphatic acids such as stearic acid or linoleic acid do not
5 act as CBR activating agents, even though for various other purposes they would be classified within the same generic class.

Naturally occurring precursors of said CBR activating agents
10 can also be employed herein, generating the activating agent for example by hydrolysis on the skin.

Mixtures of two or more of said can be employed herein, such as a combination of palmitoylethanolamide with an
15 aforementioned glycerol derivative, for example in a weight ratio of from 10:1 to 1:10.

The amount of CBR activating agent (iii) in the invention compositions is preferably selected in the range of from at
20 least 0.05%, and often to not more than 20%, more preferably in some embodiments from 0.1% and in those or other embodiments up to 10%, as herein being by weight based on the formulation or base formulation, as the case may be, unless otherwise stated. In a number of practical formulations, the
25 concentration of CBR activating agent is not more than 5%, and particularly from 0.25 to 2 wt%.

An antiperspirant composition according to the invention comprises an antiperspirant active comprising an aluminium
30 and/or zirconium salt or complex (i). The proportion of antiperspirant active present in the composition according

to the invention may be from 1-35% by weight of the composition, preferably at least 5% by weight and more preferably 15-30% by weight of the base composition. A base composition herein excludes any propellant which may be
5 employed.

Examples of suitable actives (i) include aluminium salts, zirconium salts, aluminium and/or zirconium complexes, for example aluminium halides, aluminium hydroxy halides,
10 zirconyl oxyhalides, zirconyl hydroxyhalides, and mixtures thereof. Specific examples include activated aluminium chlorohydrate, aluminium chlorohydrate, aluminium pentachlorohydrate and aluminium zirconium chlorohydrate. Useful zirconium salts include zirconium hydroxy-chloride
15 and zirconium oxychloride. Other generally used actives will be known to those skilled in the art. Preferred actives include ZAG (Zirconium Aluminium Glycine), AAZG (Activated Aluminium Zirconium Glycine), and AACH (Activated Aluminium Chlorohydrate). The antiperspirant active can be
20 present in particulate form whereupon it is normally suspended in a suitable carrier fluid, which usually is water-immiscible, and which can be structured or thickened. Alternatively the active can be dissolved in a polar solution, such as for example in aqueous solution or in a
25 polar low weight polyhydric alcohol such as propylene glycol, advantageously 30 to 60% by weight solution.

It is a benefit of the present invention that incorporation of a CBR activating agent in an effective amount can improve
30 the acceptability of conventional antiperspirant-containing

formulations, such as those containing an astringent antiperspirant active, by reducing the risk of irritancy.

The deodorant compositions according to the present invention normally comprise 0.01 to 90% of a deodorant active. Deodorancy can be provided by the aforementioned aluminium and/or zirconium antiperspirant salts or complexes, optionally with an additional deodorant active, such as any deodorant active known in the art such as alcohols, in particular aliphatic monohydric alcohols such as ethanol or propanol, antimicrobial actives such as polyhexamethylene biguanides eg those available under the trade name Cosmocil™ or chlorinated aromatics, eg triclosan available under the trade name Irgasan™, non-microbiocidal deodorant actives such as triethylcitrate, bactericides and bacteriostatis. Yet other deodorant actives can include zinc salts such as zinc ricinoleate.

The antiperspirant active salt or complex (i) and the CBR activating agent (iii) can conveniently be employed in a weight ratio of from 1:1 to 100:1, often at least 5:1, and in many instances up to 50:1.

The carrier material for the compositions according to the invention can comprise one or more of volatile carrier fluids, one or more of non-volatile emollients, and it can be structured or thickened by one or a combination of thickener and/or structurant materials if required. The carrier material, including, where relevant, carrier materials providing additional properties such as emolliency, can often comprise up to about 99 wt%, in many

instances from 5 to 90 wt% and particularly from 10 to 70 wt% of the composition, or of the base composition, if mixed subsequently with a propellant. Where the composition comprises both hydrophilic and hydrophobic phases, the weight ratio of the two phases is often in the range of 10:1 to 1:10. Aerosol compositions according to the present invention can conveniently be obtained by introducing a base formulation as described herein that is free from propellant and at least 0.7 times and often 1.5 to 20 times its weight of propellant into a suitable aerosol dispenser.

The antiperspirant or deodorant composition can comprise a mixture of particulate solids or a suspension of solids in a liquid medium, which can be thickened to reduce the rate of segregation or structured to produce a cream (soft solid) or solid. Alternatively the composition can comprise a mixture of liquid constituents, including a solution of an active in a carrier, such a composition often adopting the form of an oil-in-water or water-in-oil emulsion, which may be thickened or gelled.

The carrier material, which may be a fluid or a mixture of fluids, is often selected according to the physical form of the cosmetic composition, e.g. volatile low viscosity silicones, low molecular weight hydrocarbons, alcohols and water, and can be selected by those skilled in the art to provide appropriate physical and sensory properties for the product. It will be understood that certain fluid alcohols such as in particular ethanol can constitute both a carrier and a deodorant active simultaneously, though advantageously

formulations containing such a material also contain an additional deodorant and/or antiperspirant active.

Volatile silicones are usually selected from cyclic polysiloxanes containing from 3 to 8 dialkylsilicone groups, especially dimethylsilicone groups and particularly 4 or 5 dimethylsilicone groups. Other useful volatile silicones can comprise linear polysiloxanes, preferably containing 4 or 5 alkylsiloxane groups, including terminal groups. Low molecular weight liquid hydrocarbons can comprise paraffin oils. Suitable alcohols can comprise monohydric alcohols, such as C3 to C10 aliphatic alcohols, dihydric alcohols such as glycol or propylene glycol or polyhydric alcohols such as glycerol or sorbitol. Carrier materials can provide additional desirable properties, such as polyhydric alcohols for example glycerol can act as a moisturising agent and volatile cyclomethicones can act as emollients.

The non-volatile emollient, if used in the composition, may consist of a single emollient compound or a mixture of emollients. Such emollients often have a solubility parameter of below 10 and many of from 5.5 to 9. They can typically include saturated fatty acids and fatty alcohol esters, ethers containing aliphatic and a polyalkylene group, hydrocarbons, water insoluble ethers, mineral oils and polyorganosiloxanes, and mixtures thereof.

Non-volatile silicones are often polyalkylsiloxanes, polyalkylarylsiloxanes or polyethersiloxanes having a viscosity of above 10 mPa.s, such as up to about 5×10^6 mPa.s

at 25°C, including polymethylphenylsiloxanes or dimethylpolyoxyalkylene ether copolymers.

Emollient aliphatic esters, often containing from about 12
5 to 25 carbons, and preferably one substituent containing a
chain of at least 12 carbons. Examples include cetyl
palmitate, butyl myristate, glyceryl stearate and propylene
glycol monolaurate. The composition can comprise a liquid
aliphatic ether which can provide emolliency, such as ethers
10 derived from polyalkylene glycols and a low weight (eg up to
C6) alcohol, such as polypropylene glycol (10-15) butyl
ether.

The total amount of emollient materials within the
15 composition is often within the range of from 1 to 70 wt%.

The thickening or structurant agent, when required, is
selected according to the product form of the cosmetic
composition. The thickening or structuring agent can be
20 organic (monomeric or polymeric) or inorganic and is usually
chosen depending on the physical nature of the liquid phase
to be thickened or structured, such as whether it is
hydrophobic or hydrophilic. The amount is normally selected
in order to attain the desired viscosity of the liquid or
25 cream or desired resistance to penetration of a solid
containing the PPAR fatty acid or precursor thereof in
accordance with the present invention.

The thickener or structurant can be any of a number of
30 materials, including, for example, waxy structurants for a
formulation containing a water-immiscible phase including

hydrogenated vegetable oil, hydrogenated castor oil, fatty acids, such as 12-hydroxystearic acid (12-HSA), or ester or amide derivatives of such acids, beeswax, paraffin wax, microcrystalline waxes, silicone wax, and fatty alcohols, such as stearyl alcohol. The structurant can also be a fibre-forming gellant, of which 12-HSA is an example. Other examples include N-acyl amino acid amides and esters, including particularly GP-1 (N-Lauroyl-L-glutamic acid di-n-butylamide), lanosterol, combinations of a sterol and a sterol ester, such as especially β -sitosterol and χ -oryzanol, a polyesterified cellobiose, especially with a C8 to C10 aliphatic acid, threitol esters or and selected secondary amides of di or tri basic carboxylic acids, (eg 2-dodecyl-N,N'-dibutylsuccinimide) by themselves or in combination.

Polymeric materials for thickening include polymers such as polyamides, hydroxypropylcellulose, and natural or synthetic gums, such as polyglycerides including agar, agarose, pectin, or guar or mixtures or combinations thereof. One class of materials worthy of attention for thickening a water-immiscible phase comprises derivatives of hydrolysed starch or other polysaccharides, including in particular esterified dextrans, such as dextrin palmitate. A further class of polymers that is particularly directed to structuring an oil phase containing a silicone oil comprises polysiloxane elastomers. Suspending agents such as silicas or clays such as bentonite, montmorillonite or hectorite, including those available under the trademark Bentone can also be employed to thicken liquid compositions according to the invention. The composition can be thickened with non-

polymeric organic gellants, including selected dibenzylidene alditols (eg dibenzylidene sorbitol).

The amount of structurant or thickening agent that can be employed in the invention compositions will depend upon the viscosity of a fluid formulation or extend of hardness of a solid formulation that the producer wishes to attain. The amount to be employed will in practice also vary depending on the chemical nature of the structurant or thickening agent. In many instances, the amount of structurant or thickening agent will be selected in the range of from 0.1 to 25 wt%, and particularly from 1 to 15 wt%.

The composition according to the invention can optionally comprise other ingredients, in addition to those already identified, depending on the nature and form of the finished product.

Other ingredients contemplated within the personal deodorant or antiperspirants art can also be included in the compositions according to the invention. These include, for example, surfactants/wash-off agents, fillers, fragrances, antioxidants, preservatives and colouring agents. Such ingredients and their amounts of use are usually selected according to the physical and chemical form of the cosmetic composition.

Surfactants can comprise optionally up to 15%, more commonly up to 5% by weight of the total product, and are particularly useful in formulating emulsion antiperspirant or deodorant compositions, for example for use as pump spray

or roll-on formulations. However for other product types, it is preferred that the composition contains less than about 8% by weight of surfactants. Non-ionic surfactants are particularly preferred. It is often convenient to
5 select a mixture of surfactants, such as one having a comparatively high HLB value, eg 8 to 18, and one having a comparatively low HLB value, eg 2 to 8, which can be introduced in suitable relative proportions to to attain an average HLB value of about 6 to 12.

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Many suitable nonionic surfactants are selected from nonionic esters, ethers or amine oxides having an appropriate HLB value. Many preferred ionic surfactants comprise a polyoxyalkylene moiety, especially a
15 polyoxyethylene moiety eg 2 to 80, especially 5 to 60 oxyethylene units, or possibly with a polyoxypropylene content, to provide hydrophilicity. Other moieties providing hydrophilicity include polyhydric alcohols such as sorbitol or glycerol. The hydrophobic moiety is commonly
20 derived from aliphatic alcohols or acids or amines containing about 8 to 50 carbons and particularly 10 to 30 carbons. Examples of suitable nonionic surfactants include cetareth-10 to -25, ceteth-10 to -25, steareth-10 to -25, and PEG-15 to -25 stearate or PEG-8 distearate. Other
25 suitable examples include C10-C20 fatty acid mono, di or tri-glycerides. Further examples include C18-C22 fatty alcohol ethers of polyethylene oxides (8 to 12 EO).

Examples of surfactants which typically have a low HLB
30 value, often from 2 to 8, can comprise mono or possibly di fatty acid esters of polyhydric alcohols such as glycerol,

sorbitol, erythritol or trimethylolpropane, including cetyl, stearyl arachidyl and behenyl derivatives.

5 Fillers can comprise up to about 20%, more commonly up to 10% of the base composition and can act as supports for liquid ingredients. Suitable fillers include aluminium stearate, aluminium tri-stearate, calcium stearate, talc or finely divided polyethylene, an example of which is ACUMIST B18. The latter can also enhance skin feel properties.

10 Fragrances, when present, typically comprise up to about 4% of the total product and often from 0.1 to 1.5%.

15 Colouring agents antioxidants such as ascorbic acid and tocopherol and preservatives such as C1 to C3 alkyl parabens can be added as desired.

20 Other optional ingredients are other cosmetic adjuncts conventionally employed or contemplated for employment in antiperspirant or deodorant products.

The ingredients which can optionally be present in the composition carrier can conveniently form the balance of the composition.

25 Propellants commonly employable in aerosol compositions herein commonly comprise hydrocarbons or halohydrocarbons such as fluorohydrocarbons, having a boiling point of below 10°C and especially those with a boiling point below 0°C. It is especially preferred to employ liquified hydrocarbon
30 gases, and especially C₃ to C₆ hydrocarbons, including

propane, isopropane, butane, isobutane, pentane and isopentane and mixtures of two or more thereof. Preferred propellants are isobutane, isobutane/isopropane, isobutane/propane and mixtures of isopropane, isobutane and butane. Other or additional propellants include fluorinated low molecular weight hydrocarbons. Yet still other propellants can include volatile ethers or carbon dioxide.

The relative weight proportions of propellant and base composition is often selected at least 40:60 and particularly at least 60:40. The proportions in many embodiments are up to 99:1 and particularly up to 95:1. Commonly, proportions are selected in the range of at least 70:30 and in the same or other formulations the proportions are up to 90:10.

Compositions according to the invention can be provided in any form of a product suited to or adapted for topical application to human skin, and is usually contained in a suitable holder or dispenser to enable it to be applied to the selected area of the skin, particularly the underarm, where control of perspiration and/or deodorancy is desired.

Having described the invention in general terms, specific embodiments thereof will now be described in greater detail by way of example only.

Example 1

Effect of topically applied HU-210 on histamine-induced itch.

In this demonstration, a material was tested to see if it was a CBR activating agent. HU210 was dissolved in Aqueous Cream BP at a concentration of 0.5% and 0.05% (w/v) and topically applied to the volar forearm skin: five applications of 50µl per 3 cm² area, and itching perception was determined after 4 hours. The control site contained the vehicle alone and the study was performed in a double-blind fashion. The cream covered area was then treated with histamine applied by iontophoresis to induce itch. In summary, a 1% histamine solution in 1% methylcellulose was placed in the iontophoretic chamber and a 10 sec burst of 50µA was applied using an Iontophoresis Controller MIC-e (Moors Instruments, of Axminster, U.K.). After application of the current, each subject indicated the intensity of the itch sensation, by moving a slider to the appropriate point on a Visual Analogue Scale (VAS), which ranges from threshold sensation (0) to maximal itch (10), to indicate the subject's itch response. VAS readings were taken for 5 minutes following histamine application and plotted against the time of the reading. The VAS value shown in subsequent tables of results comprises the area under the curve from 0 to 5 minutes. The results are summarised in Table 1 below. The formulation of the Aqueous Cream B.P. comprised:

- cetylstearyl alcohol 8.1%w/w
- sodium lauryl sulphate 0.9% w/w
- liquid paraffin 6.0%
- white soft paraffin 15.0% w/w
- water - balance.

Table 1

Treatment			Itch score (area under the curve)	Itch score % of control
	Vehicle	HU-210 amount		
Control	yes	0	1634	100
1.1	yes	0.05%	101	7.3
1.2	yes	0.5%	119	6.2

The results in Table 1 show that HU-210 is capable of reducing histamine-induced itch when topically applied and is indicative of the capability of CBR activating agents to alleviate itch.

Example 2

- 10 Effect of Palmitoylethanolamide applied by patch on histamine-induced itch.

In this demonstration of whether a test material was a CBR activating agent, the method of Example 1 was followed except for employing palmitoylethanolamine (PEA, 100mM) in 50% ethylene glycol: 50% ethanol instead of HU-210 (in an aqueous Cream BP) at the specified concentration, and applied to the skin under a water-impermeable patch for 24 hours before the histamine challenge. The method was carried out four times. The results are summarised in Table 2 below.

Table 2

Treatment		Itch score (area under curve)	Itch score % of control
Control	Vehicle alone	500	100
2.1	Vehicle + PEA	129	26
Control	Vehicle alone	377	100
2.2	Vehicle + PEA	103	27
Control	Vehicle alone	701	100
2.3	Vehicle + PEA	545	78
Control	Vehicle alone	56	100
2.4	Vehicle + PEA	32	57

From Table 2, it can be seen that the CBR activating ligand
5 PEA can inhibit histamine-induced itch. The population
exhibits a wide variation in response to histamine-induced
itch. The same trend was observed for subjects who on
average exhibited higher responses to the histamine-induced
itch as for those who exhibited a much lower response.

10

Example 3

Effect of topically applied Palmitoylethanolamide on
histamine-induced itch.

15

In this demonstration, Palmitoylethanolamide (50mM in
ethanol) was mixed with Vaseline Intensive Care TM Lotion
(abbreviated to VICL) (volume ratio 1:1). This mixture was
applied (250 μ l/ 5cm² - 5 times at 1h intervals) and histamine

iontophoresis was performed on the treated site in the method described in Example 2. The vehicle control was ethanol:VICL (volume ratio 1:1). The procedure was carried out thrice, and the results summarised in Table 3 below.

5

Table 3

Treatment		Itch score (area under the curve)	Itch score % of control
Control	Vehicle alone	3590	1000
3.1	Vehicle + PEA	1186	33
Control	Vehicle alone	622	100
3.2	Vehicle + PEA	103	16.5
Control	Vehicle alone	264	100
3.3	Vehicle + PEA	211	79.7

The results in Table 3 show that PEA can inhibit histamine-induced itch when topically applied to the skin in the presence of a lotion. This response occurs irrespective of whether the subjects were high or low itch responders.

10

Example 4 (Comparison)

Effect of topically applied N-acyl ethanolamides on histamine-induced itch.

15

Related molecules stearylethanolamine (SEA; 50mM in ethanol) and linoleoylethanolamine (LAMEA; 50mM in ethanol) were tested as potential activating agents for a CBR, employing the test method described in Example 3 and applied in the

20

ethanol:VICL lotion. The results are summarised in Table 4 below

Table 4

Treatment		Itch score (area under the curve)	Itch score % of control
Control	Vehicle alone	1770	100
4.1	Vehicle + SEA	3354	190
4.2	Vehicle + LAMEA	1768	100
Control	Vehicle alone	210	100
4.3	Vehicle + LAMEA	356	169
4.4	Vehicle + SEA	485	231
Control	Vehicle alone	1383	100
4.5	Vehicle + SEA	3593	260
4.6	Vehicle + LAMEA	1497	108

- 5 From Table 4, it can be seen by comparison with the relevant control that other N-acyl ethanolamines SEA and LAMEA were unable to demonstrate any anti-pruritic action or even appeared to exacerbate the itch response.

10 Example 5

Skin Organotypic Culture Analysis of Palmitoylethanolamide.

In this Example, skin organotypic cultures (Epiderm™, MatTek Inc, USA) were treated topically with an antiperspirant
15 formulation (abbreviated to APF1) which is summarised in

Table 5 below. Palmitoylethanolamide (PEA) was introduced into the medium. The cultures were then incubated at 37°C, 5% CO₂, and 95% relative humidity (standard cell culture conditions) for 24h. The culture medium was assayed for the pro-inflammatory cytokine interleukin-6 (IL-6). After water washing to remove the AP formulation, the viability of the culture was determined using the MTT assay. IL-6 was determined using an ELISA assay (R&D systems). The results are summarised in Table 6.

10

Table 5

Trade Name	INCI Name	Supplier	% w/w
Rezal 67	Al-Zr Pentachloro-hydrate (40%)	Reheis	50.00
Distilled Water	Water		35.45
DC245	Cyclomethicone	Dow Corning	4.00
Emulgade SE	Glyceryl Stearate, Ceteareth-20, Ceteareth-12, Cetearyl Alcohol, Cetyl Palmitate	Cognis	2.00
Structure Solanace	Amphoteric Potato Starch	National Starch	1.00
	Parfum		1.00
Polawax GP200	Cetearyl Alcohol, PEG 20 Stearate	Croda	0.65
Cutina MD	Glyceryl Stearate	Cognis	1.00
Eumulgin B2	Ceteareth-20	Cognis	0.40
Eutanol G	Octyldodecanol	Cognis	0.50
Glycerol	Glycerine	Unichema	4.00

Table 6

Treatment	APF1	PEA amount	IL-6 pg/ml \pm SD
Base	no	no	29.8 \pm 3.5
Control	yes	no	86.3 \pm 13.2
5.1	yes	0.1 μ M	38.3 \pm 7.6
5.2	yes	1.0 μ M	36.5 \pm 11.6
5.3	yes	10.0 μ M	59.5 \pm 13.8
5.4	yes	100.0 μ M	43.0 \pm 7.9
5.5	yes	1000.0 μ M	63.0 \pm 24.8

From Table 6, it can be seen that PEA, at all concentrations used, was found to significantly decrease AP-induced IL-6 release from the cultures using Dunnet's test with a significance value of $p < 0.05$. The reduction in the pro-inflammatory cytokine IL-6 indicates that the PEA will inhibit APF1-induced irritation. Culture viability of APF1 treatment alone was not significantly different from those of a combined APF1 and PEA treatment.

Example 6

Effect of Palmitoylethanolamide on Antiperspirant-induced irritation in vivo.

In this Example, patch tests were performed on a mixed panel of 49 volunteers with age ranges between 18 and 55, using a double-blind protocol with randomized patch sites. Samples (20mg) were applied to a filter paper that was placed within a Finn chamber (0.8cm internal diameter). The chambers were

then attached to the volar forearm using Scanpore™ tape (Norgesplater, Nor.) and left for 47h. At the end of the 47h period, the patches were removed and the site was left open for 5h when the erythema associated with the patch was visually assessed and scored using an in-house standard assessment Patch Grading Scale as set out below. The results are summarised in Table 7 below.

Table 7

Treatment	APF1	PEA amount	Mean Irritation Score
Base	no	no	0.28
Control	yes	no	0.67
6.1	yes	0.25%	0.54

10

From Table 7 5, it can be seen that the APF1 formulation (a roll-on lotion) produced a significant increase in irritation score compared with no treatment - the base. Irritation was significantly mitigated by the incorporation of 0.25% palmitoylethanolamide into the base formulation. Statistical analysis was performed using a Wilcoxon signed rank test with a significance level of 5%. The conclusion from this analysis is that the irritation induced by patching the antiperspirant APF1 lotion was reduced significantly by the palmitoylethanolamide.

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Example 7

Effect of topically applied Anandamide (AEA) on histamine-induced itch.

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The demonstration method of Example 1 was followed except that AEA ((all Z)-N-(2-Hydroxyethyl)-5,8,11,14-eicosatetraenamide) was dissolved in Aqueous Cream BP at a concentration of 5% (w/v) instead of PEA. The results are summarised in Table 8 below.

Table 8

Treatment			Itch score (area under the curve)	Itch score % of control
	Vehicle	AEA amount		
Control	yes	0	1735	100
7.1	yes	5%	1322	76

From Table 8, it can be seen that the cannabinoid agonist anandamide is an inhibitor of histamine-induced itch when topically applied.

Methodology and Grading Scale

15 Histamine Iontophoresis Methodology

Histamine was applied iontophoretically to the skin using an Iontophoresis Controller MIC-e (Moor Instruments Ltd., Axminster) (Magerl, W., et al, J Invest.Dermatol., 94, 347-352 (1990)). The iontophoresis chamber was attached to the volar forearm using circular double adhesive rings. Histamine dihydrochloride (1%) dissolved in a methylcellulose gel (1%) in distilled water, was placed in the reservoir of the iontophoresis chamber and a platinum electrode in the chamber was connected to the positive

terminal of the voltage source and a reference electrode (ECG electrode) fixed to the hand served as a cathode. One Laser Doppler probe (Channel 1) was inserted into the centre of the iontophoresis chamber to measure the changes in blood flow at the application site. A second Laser Doppler probe (Channel 2) was placed 1.5cm distal to the stimulated area to assess the neurogenic mediated flare response. The probes were attached to DRT4 Dual Channel Laser Doppler Blood Flow Monitor that monitored continuously skin temperature and skin blood flow using solid-state lasers (MBF3D, Moor Instruments Ltd.). Measurements were taken for 60sec prior to insertion of the histamine solution into the chamber. This was followed by a 10sec period of 50 μ A charge delivery, which applied 0.03 micromoles (0.57 μ g) histamine into the skin. Blood flow was monitored continuously during an observation period of 5min at a frequency of 40Hz.

The subjects rated the itching sensation throughout the experiment by using a visual analogue scale (VAS), the output of which was monitored concurrently with blood flow changes. The subjects were instructed to assess the magnitude of the perceived pruritus (itch) on a linear analogue scale with the endpoints of 1 to 10, representing 'no itch' and 'unbearable itch' respectively. An intermediate reference point was set at 30% of the maximum, 4, representing the sensation of pruritus eliciting a desire to scratch the skin. VAS readings were taken for 5 min following histamine application and are expressed as area under the curve. Anti-itch agents were defined as materials which gave values of 80% or less compared with the vehicle alone.

Grading Scale for Patch and Cream CoverTable 9

	Description Grade
0.0	No apparent cutaneous involvement.
0.5	Faint, barely perceptible erythema or slight dryness
1.0	Faint but definite erythema, no eruptions or broken skin or no erythema but definite dryness; may have epidermal fissuring.
1.5	Well defined erythema or faint papules with definite dryness, may have epidermal fissuring.
2.0	Moderate erythema, may have very few papules or deep fissures, moderate to severe erythema in the cracks.
2.5	Moderate erythema with barely perceptible oedema or severe erythema not involving a significant portion of the patch (halo effect around the edges), may have a few papules or moderate to severe erythema.
3.0	Severe erythema (beet redness), may have generalized papules or moderate to severe erythema with slight oedema (edges well defined by raising).
3.5	Moderate to severe erythema with moderate oedema (confined to patch area) or moderate to severe erythema with isolated eschar formations or vesicles.
4.0	Generalized vesicles or eschar formations or moderate to severe erythema and/or oedema extending beyond the area of the patch.

Further examples of formulations according to the present invention are described hereinafter.

In the subsequent Tables herein, the following abbreviations

5 are employed

	AACH	Activated aluminium chlorohydrate
	ACH	Aluminium chlorohydrate
	AZH	Aluminium Zirconium chlorohydrate
	AZAG	Aluminium Zirconium Chlorohydrate Glycine complex
10	PHMB	Polyhexamethylene biguanide - Cl or Stearate salt
	EDTA	Ethylene diamine tetraacetic acid
	DEA	Diethanolamide
	POE	polyoxyethylene

Lotion Formulations

Table 10

Example No	8.1	8.2	8.3
Constituent	Per cent by weight		
Example No	4	5	6
Ethanol		30	
Isopropanol	30		
Hydroxypropyl-cellulose	0.7	0.7	
ACH	20		
AZH		20	
AZAG			20
PHMB			
Triclosan			
Palmitoylethanolamide	1.0	1.2	1.5
Suspending Agent			3
Propylene Carbonate			1
Glycerol	2	2	
Talc			6
Water + minors	to 100	to 100	
Cyclomethicone DC245 + minors			to 100

Lotion formulations can be applied using a roll-on, or with
 5 the exception, in some countries, of zirconium salt-containing formulations, by a pump spray.

Stick Formulations

Table 11

Example No	9.1	9.2	9.3	9.4	9.5	9.6
Constituent	% by weight					
Cyclomethicone (DC245)	39.8	36.8	35.8	39.9	39.75	46.5
Permethyl 103A	16	12				
Mineral Oil			11.5			
PPG-14 Butyl ether		4		10		
Dimethicone (50cs)			1.5			
Stearyl alcohol	14	14	14	17	11.5	
Castor wax	2	5	4.5	2.5	5	
12-hydroxystearic acid						6
N-lauroyl glutamic acid						2
Dibutylamide						
Eicosanol	0.2	0.2	0.2			
Octyldodecanol					14	14
C20-40 alcohols						0.5
C20-40 pareth-3/C20-40 pareth-20					1.75	
PEG-8 distearate				0.6		5
Al-Zr Gly antiperspirant active	23	25		24	26	26
Aluminium chlorohydrate			26			
Glycerol			2	2		
EDTA					1	
Talc	3		1.5			
Fumed Silica		1	1	2		
palmitoyl ethanolamide	1	1	1	1	1	1
Fragrance	1	1	1	1		

Table 11 (cont)

Example No.	9.7	9.8	9.9	9.10
Constituent	% by weight			
Cyclomethicone (DC245)	48	10	37	
Polydecene		12.7		
PPG-14 Butyl ether		2.5		
C12-15 alkyl benzoate			15	
propylene glycol				48.3
ethanol				13
isostearyl alcohol				12
dextrin palmitate	10			
cellobiose octanonoate		3.8		
beta sitosterol			2.5	
oryzanol			2.5	
dibenzylidene sorbitol				3
Isopropyl myristate	10			
Cetyl dimethicone copolyol		1	1	
Amino-2-methyl-1-propanol				0.2
Al-Zr Gly antiperspirant active				22.5
Aluminium chlorohydrate	30			
Zirkonal 50		51.7	40	
Glycerol		17.3		
palmitoyl ethanolamide	1	1	1	1
Fragrance	1		1	

Cream or Soft Solid formulations

Table 12

Example No	10.1	10.2	10.3	10.4	10.5	10.6	10.7
Ingredients	% by weight						
Silicone wax		2.5				3	
Syncrowax ERLC (13)			2.5		5		
Syncrowax HGL-C					1.25		
Castor wax			7.5				
Triaccontenyl vinyl pyrrolidone copolymer	5						
Paraffin wax	5	7.5					
Silica			1			1.5	1.5
Talc					1.75		6
Hydrohobic Clay							3
Bentone 38							6
Anhydrous aluminium silicate							6
Microthene powder							6
Propylene Carbonate							1.5
Cyclomethicone		63.5			60.5	62.5	38.3
Tetraphenyl tetramethylsiloxane				52			
C12-15 Alkyl benzoate	63.5		62.5			10	
Dextrin palmitate				5			
Octyldodecanol				15			
Dimethicone 10 cst					5		10
POE 100 stearyl ether							2
AACH	25	25.5				22	
Milled AACH			25.5	25.5			
AZAG 7167					25		26.7
Palmitoyl ethanolamide	1	1	1	1	1	1	1
Fragrance	0.5				0.5		

Table 12 (cont)

	10.8	10.9	10.10	10.11	10.12	10.13
Ingredients	% by weight					
Cetearyl dimethicone /vinyl dimethicone crosspolymer and Cyclopentasiloxane						62.1
Syncrowax ERLC (13)					3.75	
Castor wax	4				1.25	
Stearyl alcohol	6					
Candelilla wax		7				
C24/28 alkyl dimethicone wax		3.5				
Silica						0.2
Talc	5					
Hydrohobic Clay Bentone 38		0.5				
Cyclomethicone	58	45	49.8	-		
C12-15 Alkyl benzoate			12.7	62.5	63.5	4
Dextrin palmitate			10	10	5	
Neopentyl Glycol Diheptanoate						5
PPG14 Butyl ether	4.5					
Dimethicone 350 cst		25				
PEG8 distearate						2
Stearyl dimethicone						0.75
POE 100 stearate	1					
PPG1-PEG9-lauryl glycol ether						2
AACH			-		25.5	
Milled AACH				26		
ACH		18	-			
AZAG 7167	20		26.5			22.45
Palmitoyl ethanolamide	1	1	1	1	1	1
Fragrance	0.5			0.5		0.5

Aerosol Formulations

Table 13

	11.1	11.2	11.3	11.4	11.5	11.6
Constituents	% by weight					
Cyclomethicone DC245	3.5	11.95	14.8	3.8	4.6	5.6
Ethanol			20			
Isopropylpalmitate			10.5		9.4	
Isopropyl myristate						0.31
PPG-14 Butyl ether	9.7	0.7				9.7
Octyldodecanol		0.25				
Polydecene						0.3
Dibutyl phthalate					4.5	
Quaternised Clay - Bentone 38	1	1	1.5	1	0.95	0.7
Propylene carbonate					0.15	
Methylpropanolamine						0.08
Silicone gum (Q2- 1401)				0.2		
AACH		10		4		
Milled AACH	10					2
ACH			9.2		9.3	
Silica		0.1				0.01
Talc			3			
Micronised polyethylene					9.3	
Perfume	0.5	0.7	0.7	0.7		1
Allantoin					1.5	
Palmitoyl ethanolamide	0.3	0.3	0.3	0.3	0.3	0.3
n-Pentane				20		
C3/C4 hydrocarbon mixture	75	75	40	70	60	80

The cyclomethicone DC245 in the formulations in Tables 10, 11, 12 or 13 hereinabove can be replaced wholly or partly by DC345.

Claims:

1. An antiperspirant or deodorant cosmetic composition suitable for topical application to the human skin, characterised by comprising:
 - i. an antiperspirant or deodorant active comprising an aluminium and/or zirconium salt or complex;
 - ii. a carrier for the antiperspirant or deodorant active; and
 - iii. an effective amount of a CBR activating agent.
2. A composition according to claim 1 characterised in that the amount of the CBR activating agent is selected in the range of from 0.05 to 20% by weight and preferably 0.5 to 10% by weight.
3. A composition according to either claim 1 or 2 characterised in that the CBR activating agent is selected from:-
 - 2-arachidonyl-glycerol
 - 1-arachidonyl-glycerol
 - 3-arachidonyl-glycerol
 - 2-linoleoyl-glycerol
 - 2-linolenoyl-glycerol
 - 2-eicosatrienoyl-glycerol
 - 2-eicosatetraenoyl-glycerol
 - 2-eicosapentenoyl-glycerol
 - 2-eicosaheptaenoyl-glycerol
 - palmitoylethanolamide

(6aR)-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol, sometimes called HU-210 herein;
Indomethacin morpholinylamide;
mesylate: (R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone; and
(-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol.

4. A composition according to claim 3 characterised in that the CBR activating agent is palmitoylethanolamide.
5. A composition according to any preceding claim characterised in that it comprises from 10 to 30% by weight of an antiperspirant active.
6. A composition according to any preceding claim characterised in that the antiperspirant active contains zirconium.
7. A composition according to any preceding claim characterised in that it comprises a volatile silicone carrier, preferably in an amount of from 10 to 70 wt%.
8. A composition according to any preceding claim characterised in that it comprises a structurant or thickening agent in a concentration sufficient to produce a stick or cream.

9. A composition according to any of claims 1 to 6 characterised in that comprises base composition which forms an aerosol composition together with a propellant, the weight ratio of propellant to base composition being selected within the range of from 40:60 to 99:1.
10. A method of reducing or eliminating irritancy arising from topical application of an antiperspirant or deodorant cosmetic composition comprising an antiperspirant or deodorant active comprising an aluminium and/or zirconium salt or complex and a carrier characterised by incorporating in the composition an effective amount of a CBR activating agent.
11. A method of reducing or eliminating sweat or body odour and ameliorating or eliminating concomitant irritancy by applying topically to human skin a composition containing an antiperspirant and/or deodorant active material comprising an aluminium and/or zirconium salt or complex which further contains an effective amount of a CBR activating agent.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 02/00694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/32 A61K7/34 A61K7/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 781 917 A (LUEBBE JOHN P ET AL) 1 November 1988 (1988-11-01) cited in the application	1-8, 11
Y	claims 1-4, 11; example 1	9
Y	US 3 288 681 A (ROY NETZBANDT WILLIAM ET AL) 29 November 1966 (1966-11-29) claim 1	9
A	US 5 990 170 A (DELLA VALLE FRANCESCO ET AL) 23 November 1999 (1999-11-23) cited in the application the whole document	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *G* document member of the same patent family

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Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lindner, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/00694

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte Application No

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